BIOINFORMATICS

Vol. 00 no. 00 2015
Pages 1–2

# Parameter balancing: consistent parameter sets for kinetic metabolic models

Timo Lubitz [1] and Wolfram Liebermeister [2,3]*

[1]Theoretische Biophysik, Institut für Biologie, Humboldt-Universität zu Berlin, Berlin, Germany
[2]INRA, UR1404, MaIAGE, Université Paris-Saclay, Jouy-en-Josas, France
[3]Institut für Biochemie, Charité – Universitätsmedizin Berlin, Berlin, Germany

Received on XXXXX; revised on XXXXX; accepted on XXXXX

Associate Editor: XXXXXXX

**ABSTRACT**

**Summary:** Parameter balancing is a Bayesian method to determine consistent parameter sets for metabolic models. Incomplete, uncertain kinetic data are translated into balanced parameter sets, which are complete and thermodynamically consistent. Thermodynamic and metabolomic data can also be balanced, yielding feasible metabolic states. Aside from point estimates, uncertainty ranges and correlations of the variables in question can be determined. We provide online and command line tools for Parameter Balancing, as well as Python and Matlab implementations. The tools use standard model and data formats. Prior information about biochemical constants is freely customisable by the user.

**Availability and Implementation:** Online services, code, and documentation are accessible at `www.parameterbalancing.net`. Code includes a command line tool, a Python package and a Matlab toolbox.

**Supplementary Information:** Documentation and example models can be found at `www.parameterbalancing.net`.

**Contact:** wolfram.liebermeister@gmail.com, timo.lubitz@gmail.com

## 1 INTRODUCTION

Kinetic modelling is a common approach to studying the metabolic dynamics of cells. One of the main challenges in model construction is the choice of rate laws and kinetic parameters such as Michaelis-Menten constants, catalytic rate constants, or equilibrium constants. Kinetic and thermodynamic constants have been collected in repositories such as BRENDA (Scheer *et al.* (2010)), eQuilibrator (Flamholz *et al.* (2011)), or SABIO-RK (Wittig *et al.* (2011)), and kinetic metabolic models can be populated automatically with kinetic rate laws Liebermeister and Klipp (2006a); Dräger *et al.* (2008). However, when inserting measured parameter values directly into a model, many model parameters may remain undetermined or may even be inconsistent. Typically, various parameters have not been measured or carry large experimental uncertainties (due to *in-vitro* measurements, measurements in different model organisms, and different experimental setups). Moreover, enzyme parameters can be physically dependent because of thermodynamic Wegscheider conditions and Haldane relationships (Haldane (1930)). Ignoring these dependencies can lead to thermodynamically incorrect models showing a *perpetuum mobile*-like behaviour. In principle, missing parameters can be determined by fitting a model to metabolomic time-series data (for a review, see Ashyraliyev *et al.* (2009)). For larger models, however, model fitting becomes numerically hard, parameters may not be identifiable, and in practice thermodynamic dependencies between parameters are often ignored.

Parameter balancing (Lubitz *et al.* (2010)) addresses these problems by converting measured kinetic constants into complete, consistent sets of model parameters. It accounts for dependencies between kinetic constants arising from their definition or thermodynamic laws (such as the Wegscheider conditions and Haldane relationships) and uses these dependencies to improve the calculation of mean values, uncertainties, and correlations between the parameters in question. Prior distributions are used to keep parameter values in reasonable ranges. Given the models network structure, measured kinetic parameters, and prior distributions for the kinetic constants, parameter balancing determines a multivariate posterior distribution describing all model parameters. Point estimates and uncertainty ranges for individual model parameters can be extracted from the posterior, and consistent parameter sets can be sampled to create a model ensemble representing the range of possible models compatible with available data. Each of the sampled models and metabolic states is thermodynamically consistent. Aside from kinetic constants, the method can also be applied to determine feasible metabolic states, characterised by metabolite concentrations and thermodynamic forces.

## 2 RESULTS AND IMPLEMENTATION

Parameter balancing helps modellers determine consistent kinetic parameter sets for metabolic models. We have implemented the parameter balancing algorithm as a Python package and provide a convenient online interface. While the online interface enables the user to perform parameter balancing with default configuration with a few mouse clicks, users can embed the Python code into their own modelling workflows (Stanford *et al.* (2013)). Based on a metabolic network model and a (possibly incomplete) set of kinetic constants, a table with balanced model parameters is computed. Using these model parameters a kinetic model with modular rate laws (Liebermeister *et al.* (2010)) in the standard format SBML is generated. The simple default usage can be extended by using

*to whom correspondence should be addressed

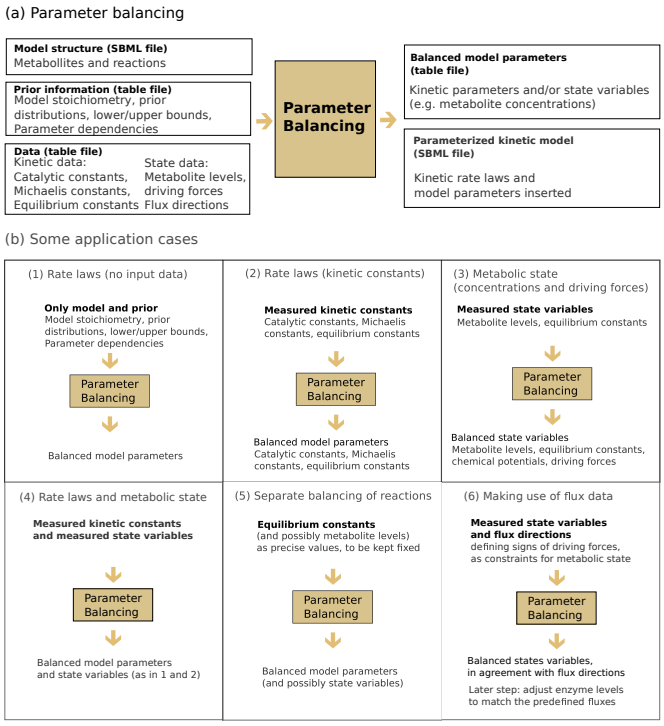


**Fig. 1.** Potential usage scenarios for parameter balancing: (1) Converting incomplete kinetic data and equilibrium constants into a balanced set of kinetic model parameters. (2) Providing metabolite levels and equilibrium constants to determine reasonable metabolic states (i.e. metabolite levels, equilibrium constants, chemical potentials, and thermodynamic forces). (3) Combining (1) and (2) for metabolic state, balanced kinetic constants, and rate laws. (4) Finding reasonable kinetic parameters for a given model stoichiometry; kinetic constant are determined from prior distributions, upper and lower bounds, and mutual parameter dependencies. (5) To simplify the calculations, parameters may be balanced separately in each reaction. In this variant of the method, equilibrium constants and metabolite levels need to be fixed to avoid inconsistencies in the resulting model. (6) If metabolic fluxes are known, the flux directions can be used to narrow down the possible metabolic states. After parameter balancing, the enzyme levels can be adjusted to match the predefined fluxes.

various configuration options. We defined biologically plausible priors for different types of kinetic constants. Instead of using these default priors, users can define their own customized priors be specifying geometric mean values, geometric standard deviations, and feasible ranges. To make the method widely applicable, we sought to support established standard formats: models are provided in SBML (Systems Biology Markup Language) format (Hucka *et al.* (2003)), and all other data are given in the table format SBtab (Lubitz *et al.* (2016)).

## 3 CONCLUSION

Parameter balancing allows modellers to translate a metabolic network into a simulatable dynamic model almost automatically. It can be integrated into modelling workflows with different kinds of available data and model parameters to be determined. As shown in Figure 1 (1), it can either be used to determine plausible default parameters (without any data, and based on prior distributions only), to balance a set of given kinetic constants, or to determine thermodynamically consistent metabolic states (comprising metabolite levels and thermodynamic forces, and accounting for known flux directions). Parameter balancing can be applied to single reactions or larger networks. Experimental data - including equilibrium constants, catalytic rate constants, Michaelis constants, metabolite and enzyme concentrations - need to be collected from literature and web resources. Adding more data will make the balanced parameters more accurate and will decrease their uncertainty ranges. Metabolic fluxes cannot be used directly as input data because the kinetic rate laws do not fit into the regression model behind parameter balancing. However, known flux directions can be used to restrict the thermodynamic forces and to narrow down the possible metabolite levels predicted by parameter balancing. The resulting state can then be matched to the given fluxes by adjusting the enzyme levels. As a potential future application, the posterior distributions obtained from parameter balancing could be used as priors for subsequent rounds of model fitting (Liebermeister and Klipp (2006b)).

*Acknowledgements* The authors wish to thank Elad Noor for pleasant and insightful discussions. [Natalie? who else?] This work was generously supported by the German Research Foundation (grant number Ll 1676/2-1 to WL).

## REFERENCES

Ashyraliyev, M., Fomekong-Nanfack, Y., Kaandorp, J. A., and Blom, J. G. (2009). Systems biology: parameter estimation for biochemical models. *FEBS Journal*, **276**(4), 886–902.

Dräger, A., Hassis, N., Supper, J., Schröder, A., and Zell, A. (2008). SBMLsqueezer: a CellDesigner plug-in to generate kinetic rate equations for biochemical networks. *BMC Systems Biology*, **2:39**.

Flamholz, A., Noor, E., Bar-Even, A., and Milo, R. (2011). eQuilibrator - the biochemical thermodynamics calculator. *Nucleic acids research*, page gkr874.

Haldane, J. (1930). *Enzymes*. Longmans, Green and Co., London. (republished in 1965 by MIT Press, Cambridge, MA).

Hucka, M., Finney, A., Sauro, H. M., Bolouri, H., Doyle, J. C., Kitano, H., Arkin, A. P., Bornstein, B. J., Bray, D., Cornish-Bowden, A., *et al.* (2003). The systems biology markup language (SBML): a medium for representation and exchange of biochemical network models. *Bioinformatics*, **19**(4), 524–531.

Liebermeister, W. and Klipp, E. (2006a). Bringing metabolic networks to life: convenience rate law and thermodynamic constraints. *Theor. Biol. Med. Mod.*, **3:41**.

Liebermeister, W. and Klipp, E. (2006b). Bringing metabolic networks to life: integration of kinetic, metabolic, and proteomic data. *Theor. Biol. Med. Mod.*, **3:42**.

Liebermeister, W., Uhlendorf, J., and Klipp, E. (2010). Modular rate laws for enzymatic reactions: thermodynamics, elasticities, and implementation. *Bioinformatics*, **26**(12), 1528–1534.

Lubitz, T., Schulz, M., Klipp, E., and Liebermeister, W. (2010). Parameter balancing in kinetic models of cell metabolism. *The Journal of Physical Chemistry B*, **114**(49), 16298–16303.

Lubitz, T., Hahn, J., Bergmann, F., Noor, E., Klipp, E., and Liebermeister, W. (2016). SBtab: A flexible table format for data exchange in systems biology. *Bioinformatics*, **32**(16), 25592561.

Scheer, M., Grote, A., Chang, A., Schomburg, I., Munaretto, C., Rother, M., Söhngen, C., Stelzer, M., Thiele, J., and Schomburg, D. (2010). Brenda, the enzyme information system in 2011. *Nucleic acids research*, page gkq1089.

Stanford, N. J., Lubitz, T., Smallbone, K., Klipp, E., Mendes, P., and Liebermeister, W. (2013). Systematic construction of kinetic models from genome-scale metabolic networks. *PLoS One*, **8**(11).

Wittig, U., Kania, R., Golebiewski, M., Rey, M., Shi, L., Jong, L., Algaa, E., Weidemann, A., Sauer-Danzwith, H., Mir, S., *et al.* (2011). SABIO-RK – database for biochemical reaction kinetics. *Nucleic acids research*, **40**(D1), D790–D796.